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PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES

MIDTERM REPORT

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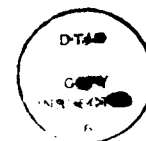
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Abstract (continued)

4. Influenza A/H3N2 was observed from mid-December until late March. However, only 35 cases occurred, with only 1 to 5 cases occurring per week. The character of the epidemiologic curve strongly indicated that the Air Force was well immunized against this virus.
5. The need for annual revaccination is predicated on antigenic drift (or shift), but also on the significant decline in antibody titer demonstrated in recruits over a 5 - month observation period. Approximately one-third of recruits had antibody levels less than the protective range to all antigens when retested in the Spring. This decline is even greater in the permanent party.
6. Vaccine efficacy against this year's epidemic strains was 67%, similar to the protective effect of the vaccine used in the prior year. Attack rates were highest (5-10%) in vaccinees with acute titers of ≤ 16 .
7. Influenza virus isolation techniques were unsatisfactory with the current epidemic strain. Antigen detection with fluorescein - labelled monoclonal antibodies was more sensitive (80%) and quicker, but serologic diagnosis remained a necessary adjunct. Future research will include evaluation of new methods for detecting viral antigen or nucleic acid.
8. In the third year since cessation of adenovirus vaccination of recruits only a single case of adenovirus infection was detected.
9. Streptococcal disease remained at a typical level (<20% of febrile URI) for the Lowry population.



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FOREWORD

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INTRODUCTION

During the 1989-90 season only the A/H3N2 influenza virus was present. Because the vaccine was fairly immunogenic in both recruits and permanent party, the Base population had relatively little illness caused by influenza virus. The civilian population also was very little affected by influenza in Colorado this past winter. This contemporary strain of influenza A has been in circulation since 1968, and the population has developed a high level of immunity.

BASE POPULATION

The composition of the Base population of Air Force personnel differed considerably from earlier years in that the number of students was down to roughly 2000 in mid February 1990. The permanent party was stable at 4124. Two cases of influenza A were detected in approximately 750 personnel from other military services on the Base. These were not included in some of the tabulations because: 1) their vaccination status could not be determined with the same accuracy as that of Air Force personnel; 2) it was often difficult to determine whether they were students or permanent party.

RESPONSE TO VACCINATION

The HI antibody response of 144 recruits who received vaccine at Lackland Air Force Base is shown in Table 1. The need for vaccination in this group is fairly obvious since 40% to 51% had antibody titers ≤ 8 to one or more antigens in the vaccine. Following vaccination, almost all were in the "protective" range with titers ≥ 32 . The results of the tests with the 3 different components were as follows:

Recruits (Table 1).

- 1) A/Shanghai/11/87 (H3N2). Before vaccination 60% of the recruits had titers ≤ 8 , and only 17% were ≥ 32 . After vaccination no persons had titers < 8 , and 93% had titers ≥ 32 .

The response to the A/Shanghai was less satisfactory than we have seen in recent years.

- 2) A/Taiwan/1/86 (H1N1). Before vaccination 53% had titers of < 8 , and only 18% had titers ≥ 32 . After vaccination no individuals had titers ≤ 8 , and 94% had titers ≥ 32 .
- 3) B/Yamagata/16/88. Before vaccination, 49% had titers of < 8 , and only 8% had titers ≥ 32 . After vaccination, 1% had titers ≤ 8 , and 93% had titers ≥ 32 .

The major change in the vaccine response was in the B component. The response to this antigen was excellent. This was the first time in several years it appeared to be better than the response to A/H1N1, and as good as that of the A/H3N2 strain.

Permanent Party.

The vaccine response in recruits has always been more favorable than in the permanent party who are being revaccinated rather than receiving primary vaccination. Because the need for annual revaccination has been repeatedly questioned, the response was studied carefully this year. Rather than receiving bloods from Lackland, as we have in the past, we arranged to study 45 permanent party volunteers at Lowry Air Force Base (Table 2).

The prevaccination sera of the permanent party showed many more with high antibody titers ("protective range") than was seen in recruits. The response to vaccine, on the other hand, was far better in the recruits, and the post vaccination level of titers was higher in the recruits, particularly with A/Taiwan. The major gain in vaccinating permanent party was that almost all individuals who had low titers showed an increase in titer of at least 2-fold; many were 4-fold. In contrast, individuals who had antibody levels ≥ 32 usually failed to show any increase in antibody titers. These data are presented in Tables 3, 4 and 5 which compare the post-vaccination HI antibody titers of persons with pre-vaccination titers to all 3 components of the vaccine.

A/Shanghai/11/87 (Table 3).

1. A/Shanghai was the virus which challenged the population at Lowry Air Force Base last year. Before vaccination, there were 7 persons who had titers in the "most susceptible" range (≤ 8), and 7 additional persons who had titers of 16. After vaccination, the number of individuals who had titers ≤ 8 was reduced to 1, and the number who had titers of 16 was reduced to 4. Three of 7 individuals who had pre vaccination titers of ≥ 32 had antibody rises of ≥ 4 -fold.

This table also shows the number and percent of persons who had increases in antibody titer of 0-fold, 2-fold, or ≥ 4 -fold. Ten of 46 individuals had increases 4-fold or higher. Thirteen of 46 (28%) had titer increases of 2-fold. Twenty-three of 46 (50%) had no change in titer. This does not necessarily mean that they did not benefit in terms of other aspects of immunity.

A/Taiwan/1/86 (Table 4)

2. The response to this antigen was not as good as with A/Shanghai. After vaccination there were 6 individuals with titers ≤ 8 , and 10 who had titers of 16. Thirty-seven percent (18 of 46) had titers ≥ 64 . This relatively poor response to the A/Taiwan component was comparable to that which we have observed during the last 3 or 4 years.

B/Yamagata/16/88 (Table 5)

3. In contrast to our experience since 1972, the response to the B component was better than to the A/H3N2. This is best illustrated by the fact that increases in titer ≥ 4 -fold were observed in 59% of persons. In addition, 15% of persons had increases in titers of ≥ 2 -fold, and only 26% had no increase in titer. All five individuals who had titers ≤ 8 before vaccination showed increases in titer between 4-fold and 32-fold. After vaccination, only 4 of 46 persons had titers of < 32 .

We note again that individuals with titers of 16 for the most part (12/15) showed an increase in antibody titer, and the same was true of individuals (16/18) with titers of 32. Whether this improvement in the response to the B component, was due to recent infection with influenza B, or to the improvement of the vaccine antigen is not clear.

Comparison of Response of Permanent Party and Recruits.

The percent of persons with titers ≤ 8 was far larger in the prevaccination sera of recruits than in the permanent party, and in addition the percent of persons with titers ≥ 32 was considerably higher after vaccination of recruits. The difference between primary vaccination response, and response to revaccination is clearly shown. This is illustrated by comparing the percent of individuals who had titers ≥ 64 . In the permanent party a response of this magnitude to A/Shanghai was seen in 62%, compared to 85% in the students. For A/Taiwan the comparison was 66% versus 83%, and with B/Yamagata the two groups were quite comparable, 73% versus 72%.

In summary, the responses to the A/Shanghai and the B/Yamagata antigens appeared to be satisfactory. The B/Yamagata component, surprisingly, was somewhat more antigenic than the A/Shanghai. The response to the A/Taiwan is particularly disappointing with a smaller percent of persons with titers > 64 . It is probable that a number of these persons lost sufficient antibody during the subsequent 3 or 4 months to enter into the susceptible range.

Cell - Mediated Immunity

Cell mediated immune responses to influenza vaccine were measured by enumerating responder T cells (influenza-specific) circulating in peripheral blood. Blood lymphocytes were obtained from anticoagulated venous blood after centrifugation on ficoll-hypaque gradients and cultured in 24 replicate wells at 60,000; 30,000; 15,000; and 7,500 cells per well, with or without influenza antigen. On the 10th day cultures were pulsed for 8 hours with 0.25 γ Ci of tritiated thymidine, cells harvested, and incorporation of isotope measured.

The number of responder cells in responding individuals is approximately 1 per 50-60,000 circulating mononuclear cells (Table 6). Prior to vaccination 40% of individuals had this many responding T cells, whereas 83% had this many responder cells after vaccination.

OCCURRENCE OF FEBRILE UPPER RESPIRATORY INFECTIONS

Overall, it was a very quiet winter at Lowry Air Force Base. (Figures 1, 2, and Table 7). There were 154 clinic visits for febrile respiratory diseases among 4124 Air Force permanent party, and 142 among 2000 Air Force students. The average weekly number of clinic visits per 1000 students during the 31 weeks of the season was .23 in the students, and .10 in the permanent party. The highest weekly rate for the students was 0.5 per/1000/week, and for the permanent party 0.3 per/1000/week.

Influenza A/H3N2 was first observed during mid-December. A few cases were observed in the permanent party every week from that time until the 26th of February, a period of 11 weeks. A single case occurred during the week of March 25th. The number of cases reported varied from 1 to 5 per week in the permanent party, and 1 to 4 per week in the student population. It was of interest that although there was a slight increase in the number of afebrile URIs, the number did not increase nearly as much as in recent years when we have had outbreaks of A/H1N1 or influenza B.

This is interpreted to be an indication that the Air Force has been well immunized against the A/H3N2 virus in recent years, and that the number of inapparent infections is relatively small. The fact that the virus continued to spread throughout the Base in the permanent party, and at the same time caused only a small number of cases each week, is compatible with this explanation. The fact that the student cases occurred at intervals of 2 or 3 weeks implies that this group is so highly immune that transmission of the virus is not supported in the student population. The few cases observed were presumably acquired from the permanent party or elsewhere in the community.

COMMENTS ON VACCINE EFFECTIVENESS

The effectiveness of the inactivated influenza vaccine in preventing illness of the influenza A virus was first demonstrated in a field trial in 1943 involving 13,000 students in ASTP units at 8 different universities. Half of the personnel in each unit received vaccine, and half received saline placebo. The protective effect was about 70%. During and after World War II a number of well controlled studies in the Armed Forces established the effectiveness of vaccine in preventing A/H1N1, A/H2N2, A/H3N2, and influenza B. During the 1960's it was considered unethical to withhold vaccine from any member of the armed services who might get influenza.

From that time on the only way to obtain assurance that the vaccine was effect was by following the incidence of the disease in various settings, and to show repeatedly that the virus did not cause illness in well vaccinated personnel. The only other useful clue, was to demonstrate a relationship between the attack rate and the HI antibody level. It has been repeatedly shown that the attack rates in "most susceptible" (HI titers of ≤ 8) individuals, is 10-25 fold greater than in persons with "protective" titers ≥ 32 .

Recruits.

Twenty-seven percent of the recruits at Lackland Air Force Base had pre-vaccination titers ≤ 8 , and only 17% had titers ≥ 32 . After vaccination the number of individuals with titers ≤ 8 were reduced to 0, and 93% had titers ≥ 32 . Recruits, based on past experience, would likely have experienced a sharp outbreak of influenza if no vaccine had been given. With vaccination, only 8 cases of influenza were detected in 2000 recruits. Four of these were in persons who had not received appropriate vaccination. One individual was completely missed. The other 3 received vaccine in August or September of the old type in which A/Sichuan was the A/H3N2 component.

It has long been known that H.I. antibody levels peak at 3 or 4 weeks after vaccination, and then fall off gradually. After 6 months the titers are reduced considerably below the post-vaccination peak. This is shown in Table 8 which compares post-vaccination titers obtained in November at Lackland Air Force Base with titers of 25 students who were bled at the clinic at Lowry Air Force Base in the Spring of 1990. These bloods were collected from students coming to the clinic for reasons other than respiratory illnesses. It is apparent that a considerable number of individuals have fallen below the "protective level".

Permanent Party - The Need for Annual Revaccination

A similar decline in antibody levels in permanent party is shown in Table 11 which compares the HI titers of 46 persons bled in the Fall with those of 25 persons 5 months later.

In the permanent party who are revaccinated each year, we have observed repeatedly that the change in antibody levels is not as great as in students who are vaccinated for the first time. Many of the permanent party showed no change in HI titer or at most 2 fold increase. However, it is clear that the few "most susceptible" individuals who have titers ≤ 8 usually show a sharp increase in titers after vaccination. The difference between the post-vaccination titers and those in 25 persons bled in April 1990 is considerably greater than that observed in the students (Table 9). For example the percent of individuals with titers ≤ 8 against A/Shanghai was 36% in the permanent party, and only 2% in students. Although, in the last few years the attack rates in the permanent party have been higher than in students, the rates of the permanent party have still been quite low.

It has been difficult to get a hard figure on how many of the permanent party received vaccine. In the past we could not obtain a good estimate of vaccine efficacy because we lacked an accurate denominator. Last year the Base Immunization Team provided us with a record of vaccination coverage by units. We reported last year that the vaccine efficacy in influenza A/H1N1 (based on 23 cases) was 69% and in influenza B (based on 16 cases) was 82%. This year the Air Force permanent party on the Base was vaccinated at an estimated rate of 93%. Twenty-seven cases were detected in the permanent party. Twenty-two had received vaccine, 5 had not. The vaccine efficacy estimated from these numbers is approximately 67% is obtained (Table 10).

While these numbers are small, when combined with those obtained in earlier years, the data suggest that the attack rates in unvaccinated permanent party were about 3 times higher than those in vaccinated persons. The protective effect of the vaccine would presumably be greater if there was more antigenic drift.

RELATIONSHIP BETWEEN HI ANTIBODY TITER AND ATTACK RATES

The estimated attack rates of influenza in the Air Force permanent party are shown in Table 11. The 27 cases which were detected occurred predominately in persons with titers ≤ 8 (10.4%), among persons with titers 16 (5.4%), and in those with a titer of 32 (0.4%). No cases were detected among 2445 persons with titers ≥ 64 . The overall attack rate was 0.7%.

In the students only 8 cases were detected (Table 12). Four of these occurred in persons with titers ≤ 8 (6.7%), 2 in persons with titers of 16 (2.5%), 1 in a person with a titer of 32 (0.6%), and 1 in a person with a titer of 64 (0.3%). The overall attack rate was 0.4%.

LABORATORY OBSERVATIONS

Influenza.

The results of virus isolation attempts in Rhesus Monkey Kidney (RMK) tissue culture compared with CF and HI tests with A/Shanghai antigen are shown in Table 13. Only 1 virus was isolated from 8 students with a virus isolate or positive serology. Thirteen virus strains were isolated from 29 similarly chosen members of the permanent party. Eleven of the 14 were positive on first passage. Twelve throat washings which had been negative on first passage were passed, and 3 additional strains were recovered. Twelve other negative throat washings were reinoculated, but no viruses were recovered.

With CF tests, 7 of 8 students had significant rises in titer, and 18 of 27 (67%) of the permanent party also had significant rises in titer. With the HI tests, 7 of 8 students had significant rises in titer, and 24 of 27 of the permanent party had significant rises in titer.

For the whole Air Force personnel, the virus isolation figure was 28%, CF tests were positive in 71%, and HI tests in 89%.

Fluorescent Antibody Diagnostic Detection

An FA test on cells obtained from throat swabs and using monoclonal antibodies detected 80% of cases proven by culture or serologic test. This rapid method was better (and quicker) than virus isolation, but still not optimal. Nonetheless, it might be useful in recognizing, and identifying an epidemic as being caused by influenza A. The specificity is very high.

Serologic Diagnosis

We compared our results of HI tests on 25 permanent party with the CDC testing of the same sera for A/Shanghai/11/87 and A/Taiwan/1/86 antibody. We

found major discrepancies between the two laboratories. We hesitate to pass on the results at the present time because we have not had an opportunity to recheck our own results, and CDC has not had a chance to compare their results with ours. In the past when we compared data with CDC we have not had differences of this magnitude.

The CDC tested the 25 serum pairs for B/Yamagata/16/88 only by neutralization test. The results of the neutralization test appeared to closely parallel results of the HI tests done here.

Other Viruses.

The role of other viruses as causes of respiratory illness was studied in some detail. No cases of influenza B were detected. One patient with a CF titer of 64, and 3 with titers of 32 were found. These are higher than CF titers normally seen 3 or 4 months after vaccination, and may represent cases of influenza B which occurred somewhat earlier.

All patients ill with URI were tested for adenovirus infection by CF test, and only one case was found, a 30 year old member of the permanent party who became ill in April 1990. His titer rose from 16 to 128. There were 4 persons who had titers of 32 in both acute and convalescent sera. They may have been infected earlier in the winter. This finding of only a single case of clinical illness is of interest, because this is now the third year since the administration of adenovirus vaccine to recruits was stopped at Lackland Air Force Base.

During this past winter we observed a considerable amount of respiratory syncytial virus disease both in infants and residents of nursing homes. We plan to screen acute and convalescent sera from all ill students and permanent party for CF antibodies to RSV and parainfluenza 1, 2, and 3. In order to conserve antigen we are initially testing convalescent sera at a titer ≥ 32 . Subsequently we plan to run all those that have titers ≥ 16 , testing acute and convalescent sera together. To date we have completed screening tests on 45 students during the period between January 1, 1990 and March 15, 1990, and have found 10 students with titers ≥ 16 for parainfluenza 3 and 7 students with titers ≥ 16 for RSV. The results of these tests will be reported as they are completed.

STREPTOCOCCAL DISEASE

Streptococcal disease has been a major interest of the Air Force since World War II when large epidemics occurred on military bases, particularly in the Rocky Mountain area, accompanied by many cases of rheumatic fever. During the first year of our studies at Lowry Air Force Base in 1952 there were more than a 100 hospitalized cases of acute rheumatic fever. The incidence of rheumatic fever fell off shortly after that, and no cases have come to our attention during the last 20 years.

Three years ago reports of acute rheumatic fever in Utah, and several other states caused renewed concern about the disease. Also, there have been reports about the unusual virulence of streptococcal infections with

streptococcal bacteremia. Two years ago we had a cluster of streptococcal pharyngitis at Lowry Air Force Base from which mucoid streptococci were isolated. These were typed by Dr. Kaplan (University of Minnesota) and found to be M type 8. This type disappeared shortly thereafter. No rheumatic fever was reported.

During the past winter surveillance at Lackland Air Force Base indicated that the rate of streptococcal carriers among recruits was high enough to warrant the administration of penicillin. Recruits who came to Lowry during January and February had already received Bicillin.

Streptococcal infections were detected almost every week during the past winter (Table 14). There has been no particular clustering of cases in time or unit. The percent of febrile URIs with positive streptococcal cultures (17%) was similar to that seen in recent years.

The incidence of streptococcal infections may have been higher than that Mr. Leroy James, formerly a Master Sergeant, who had special interest and skill in growing streptococci, had retired from the laboratory the year before. The staff has been short handed through much of the year. Cultures were not done on all individuals who came to the clinic with sore throats. As a matter of fact, early in the season when the staff person made a diagnosis of streptococcal pharyngitis, they often did not order a throat culture to confirm the diagnosis.

PERSPECTIVES ON INFLUENZA IN THE AIR FORCE

Table 15 is taken from the final report to the Army Research and Development Command for the period 1982-1988. This Table shows the number of cases of influenza (serological diagnosis and/or virus isolation) from patients who came to the clinic with a fever of $\geq 99^{\circ}$ and respiratory symptoms. The results of the 1989-1990 Season have been added.

The A/H3N2 virus is still considered to be the most virulent of the influenza viruses currently circulating through the United States. There have been 5 winters during this period when this virus subtype has appeared at Lowry Air Force Base and the surrounding community. The student population has been almost completely protected against this strain. This has been largely due to vaccination.

The permanent party has also fared quite well against A/H3N2 with 32 cases being the largest number detected in any year. This virus has now been circulating since 1968, when it first appeared as the Hong Kong strain. The permanent party has had contact with this virus and has been repeatedly vaccinated. As a result, even before vaccine is given, there is a high level of immunity. A large proportion of recruits, on the other hand, tend to have HI titers in the "most susceptible" range. Almost all have responded extremely well to vaccination, and have had titers high enough to protect them against this subtype. The uniformly good response is presumably based on previous infection with the virus.

Influenza A/H1N1, which first appeared in 1977 as the "Russian" strain, has reappeared as the A-prime virus (which first appeared in the late 1940's). The age cutoff for primary infection, which was 23-25 years of age in 1977, has now moved into the thirties, and it must be assumed that all military personnel old enough to be in the Armed Services have been infected once or more. All seemed to respond well to primary vaccination. This suggests that infection has been almost universal at sometime in the past. This virus has caused more illness in recruits than A/H3N2. The data obtained 1 year ago suggested that recruits are now better protected than in previous years.

Influenza B has been unpredictable. The vaccine response has been poor until last year when B/Yamagata was introduced as a vaccine strain. In 1985 when B/USSR was used in the vaccine there was a plethora of cases in both students and permanent party. The selection of vaccine strains for influenza B prior to 1989 does not appear to have been optimal.

PAUCITY OF ADENOVIRUS INFECTION

Adenovirus disease, which used to be the main cause of respiratory illness at Lowry Air Force Base, has almost disappeared. The Air Force stopped vaccination in recruits at Lackland Air Force Base three years ago. Adenovirus disease has not been reestablished in the student population during that time. However, the detection of an occasional case indicates that adenoviruses are still present. It is hoped that the Armed Services can maintain a relationship with the manufacturers which will insure a supply of vaccine of good quality on short notice.

FUTURE DIRECTIONS

The activity of this laboratory in the future, should, we believe include surveillance of all the viruses which cause febrile URIs. Using traditional techniques to grow viruses in tissue culture, and traditional HI and CF tests, has generally been satisfactory. We need now to utilize modern techniques for antigen detection and rapid viral diagnosis. Hopefully, we can reduce the category of diseases of unknown etiology to a very low point.

Figure 1. Outbreak of Influenza A(H3N2) in Students at Lowry AFB 89-90

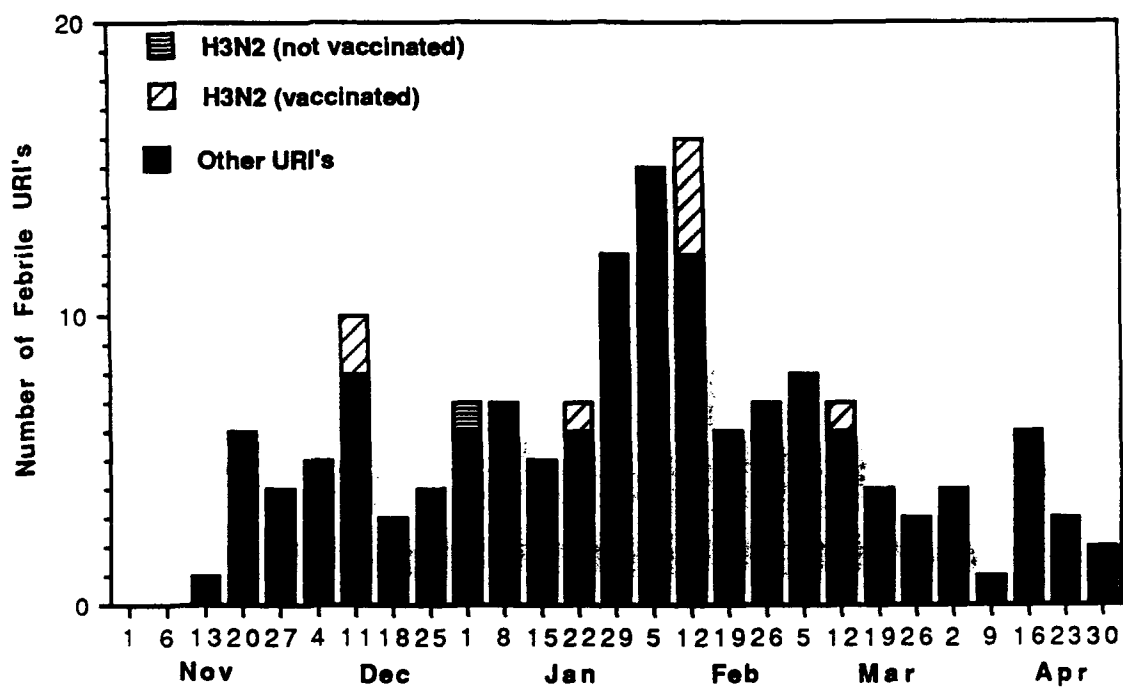


Figure 2. Outbreak of Influenza A(H3N2) in Perm. Party at Lowry AFB 89-90

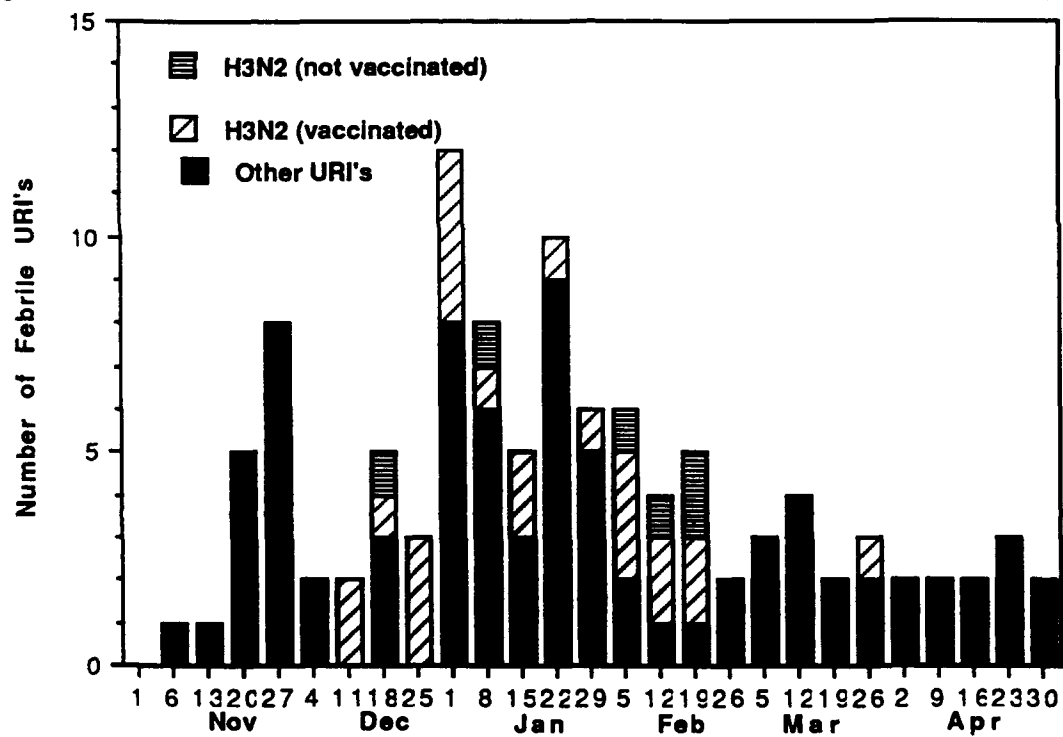


Table 1

H.I. titers of 144 recruits at Lackland AFB before and after receiving vaccine containing 15 ug each of A/Shanghai/11/87, A/Taiwan/1/86, and B/Yamagata/16/88.

| Antigen | | % of persons with HI titer \geq | | | | | | | | |
|----------------------|------------------|-----------------------------------|-----|----|-----------|----|-----|-----|-----|------|
| | | <8 | 8 | 16 | <u>32</u> | 64 | 128 | 256 | 512 | 1024 |
| A/Shanghai (H3N2) | pre ¹ | 40 | 60 | 36 | <u>17</u> | 8 | 3 | 1 | 0 | 0 |
| | post | 0 | 100 | 97 | <u>93</u> | 85 | 71 | 58 | 49 | 31 |
| A/Taiwan (H1N1) | pre | 47 | 53 | 35 | <u>18</u> | 12 | 7 | 2 | 0 | 0 |
| | post | 0 | 100 | 98 | <u>94</u> | 83 | 65 | 43 | 29 | 16 |
| B/Yamagata | pre | 51 | 49 | 21 | <u>8</u> | 2 | 1 | 0 | 0 | 0 |
| | post | 1 | 99 | 96 | <u>93</u> | 89 | 72 | 50 | 35 | 24 |

¹ Bled on 11/17/89 and 12/20/89

Table 2

H.I. titers of 46 permanent party at Lackland AFB before and after receiving vaccine containing 15 ug each of A/Shanghai/11/87, A/Taiwan/1/86, and B/Yamagata/16/88.

| Antigen | | % of persons with HI titer \geq | | | | | | | |
|----------------------|------------------|-----------------------------------|----|----|-----------|----|-----|-----|----------|
| | | <8 | 8 | 16 | <u>32</u> | 64 | 128 | 256 | 512 1024 |
| A/Shanghai (H3N2) | pre ¹ | 7 | 95 | 86 | <u>71</u> | 38 | 16 | 9 | 9 2 |
| | post | - | 99 | 97 | <u>88</u> | 62 | 27 | 10 | 6 2 |
| A/Taiwan (H1N1) | pre | 9 | 91 | 67 | <u>39</u> | 22 | 11 | 4 | 2 - |
| | post | 2 | 99 | 88 | <u>66</u> | 40 | 20 | 9 | 7 - |
| B/Yamagata | pre | 11 | 90 | 90 | <u>57</u> | 18 | 7 | 7 | - - |
| | post | - | 99 | 99 | <u>90</u> | 73 | 53 | 36 | 6 2 |

¹ Bled on 11/7/89 and 11/27/89

Table 3

Comparison of Pre and Post Vaccination H.I. Titers
of 46 Permanent Party at Lowry Air Force Base.

| A/Shanghai/ 11/87 (H3N2) | Pre Vacc. Titer | No. of Persons with Post Vacc. H.I. Titer of | | | | | | | | |
|--------------------------------|-----------------------|--|----|----|----|-----|-----|-----|------|---|
| | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| | <8 | - | - | 1 | 1 | 1 | - | - | - | - |
| | 8 | - | 1 | 2 | - | 1 | - | - | - | - |
| | 16 | - | - | 1 | 3 | 2 | - | 1 | - | - |
| | 32 | - | - | - | 7 | 5 | 3 | - | - | - |
| | 64 | - | - | - | 1 | 6 | 3 | - | - | - |
| | 128 | - | - | - | - | 1 | 2 | - | - | - |
| | 256 | - | - | - | - | - | - | - | - | - |
| | 512 | - | - | - | - | - | - | 1 | 2 | - |
| | 1024 | - | - | - | - | - | - | - | - | 1 |

Fold Increases in Titer:

| | | |
|--------|-------|-----|
| 0 fold | 23/46 | 50% |
| 2 fold | 13/46 | 28% |
| 4 fold | 10/46 | 22% |

Table 4

Comparison of Pre and Post Vaccination H.I. Titers
of 46 Permanent Party at Lowry Air Force Base.

| A/Taiwan/ 1/86 (H1N1) | Pre Vacc. Titer | No. of Persons with Post Vacc. H.I. Titer of | | | | | | | | |
|-----------------------------|-----------------------|--|----|----|----|-----|-----|-----|------|---|
| | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| | <8 | 1 | 1 | 1 | 1 | - | - | - | - | - |
| | 8 | - | 4 | 3 | 1 | 2 | - | - | 1 | - |
| | 16 | - | - | 6 | 4 | 1 | 1 | - | 1 | - |
| | 32 | - | - | - | 6 | 2 | - | - | - | - |
| | 64 | - | - | - | - | 4 | 1 | - | - | - |
| | 128 | - | - | - | - | - | 3 | - | - | - |
| | 256 | - | - | - | - | - | - | 1 | - | - |
| | 512 | - | - | - | - | - | - | - | 1 | - |
| | 1024 | - | - | - | - | - | - | - | - | - |

Fold Increases in Titer:

| | | |
|--------|-------|-----|
| 0 fold | 26/46 | 57% |
| 2 fold | 11/46 | 24% |
| 4 fold | 9/46 | 20% |

Table 5

Comparison of Pre and Post Vaccination H.I. Titers
of 46 Permanent Party at Lowry Air Force Base.

| B/Yamagata/ 16/88 | Pre Vacc. Titer | No. of Persons with Post Vacc. H.I. Titer of | | | | | | | | |
|----------------------|-----------------------|--|----|----|----|-----|-----|-----|------|---|
| | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| | <8 | - | - | 1 | 2 | 1 | 1 | - | - | - |
| | 8 | - | - | - | - | - | - | - | - | - |
| | 16 | - | - | 3 | 3 | 2 | 4 | 2 | 1 | - |
| | 32 | - | - | - | 2 | 3 | 2 | 9 | 1 | 1 |
| | 64 | - | - | - | 1 | 3 | 1 | - | - | - |
| | 128 | - | - | - | - | - | - | - | - | - |
| | 256 | - | - | - | - | - | - | 3 | - | - |
| | 512 | - | - | - | - | - | - | - | - | - |
| | 1024 | - | - | - | - | - | - | - | - | - |

Fold Increases in Titer:

| | | |
|--------|-------|-----|
| 0 fold | 12/46 | 26% |
| 2 fold | 7/46 | 15% |
| 4 fold | 27/46 | 59% |

Table 6

Cellular Immune Response After Influenza Vaccine.

| | n | Positive ¹ | Frequency of Cells in Responders |
|-------------------|----|-----------------------|-------------------------------------|
| Pre Immunization | 13 | 5 | 1:59,750 +/- 28,000 |
| Post Immunization | 12 | 10 | 1:53,900 +/- 28,000 |

¹ Defined as responder cell per 50,000 peripheral blood mononuclear cells

Table 7
No. of clinic visits and URI's with/without fever by week.

| Week Of: | Clinic Total | Afebrile URI | Total | Febrile URI's > 99.0 | | | |
|-----------|-----------------|-----------------|-------|----------------------|-------|----------|-------|
| | | | | Perm | | Students | |
| | | | | Total | Flu A | Total | Flu A |
| 1-Nov-89 | 278 | 32 | 0 | 0 | | 0 | |
| 6-Nov-89 | 384 | 35 | 1 | 1 | | 0 | |
| 13-Nov-89 | 497 | 74 | 2 | 1 | | 1 | |
| 20-Nov-89 | 399 | 28 | 11 | 6 | | 5 | |
| 27-Nov-89 | 555 | 65 | 13 | 8 | | 5 | |
| 4-Dec-89 | 494 | 40 | 7 | 2 | | 5 | |
| 11-Dec-89 | 392 | 31 | 13 | 4 | 2 | 9 | 2 |
| 18-Dec-89 | 434 | 56 | 9 | 5 | 2 | 4 | |
| 25-Dec-89 | 160 | 21 | 8 | 7 | 3 | 1 | |
| 1-Jan-90 | 314 | 31 | 20 | 10 | 4 | 10 | 1 |
| 8-Jan-90 | 501 | 23 | 17 | 12 | 2 | 5 | |
| 15-Jan-90 | 381 | 32 | 10 | 6 | 2 | 4 | |
| 22-Jan-90 | 564 | 37 | 17 | 11 | 1 | 6 | 1 |
| 29-Jan-90 | 467 | 36 | 20 | 11 | 1 | 9 | |
| 5-Feb-90 | 500 | 47 | 21 | 11 | 4 | 10 | |
| 12-Feb-90 | 515 | 44 | 20 | 10 | 3 | 10 | 4 |
| 19-Feb-90 | 461 | 26 | 11 | 7 | 4 | 4 | |
| 26-Feb-90 | 516 | 46 | 9 | 3 | | 6 | |
| 5-Mar-90 | 409 | 22 | 11 | 4 | | 7 | |
| 12-Mar-90 | 467 | 23 | 12 | 3 | | 9 | |
| 19-Mar-90 | 494 | 19 | 6 | 2 | | 4 | |
| 26-Mar-90 | 370 | 20 | 6 | 4 | 1 | 2 | |
| 2-Apr-90 | 466 | 27 | 6 | 3 | | 3 | |
| 9-Apr-90 | 441 | 37 | 4 | 3 | | 1 | |
| 16-Apr-90 | 361 | 23 | 8 | 6 | | 2 | |
| 23-Apr-90 | 435 | 21 | 6 | 4 | | 2 | |
| 30-Apr-90 | 446 | 26 | 4 | 2 | | 2 | |
| 7-May-90 | 417 | 18 | 8 | 4 | | 4 | |
| 14-May-90 | 431 | 30 | 9 | 4 | | 5 | |
| 21-May-90 | 452 | 21 | 6 | 5 | | 1 | |
| 28-May-90 | 180 | 3 | 1 | 1 | | 0 | |
| Total | 13181 | 994 | 296 | 154 | 29 | 142 | 8 |

Table 8

Comparison of One-Month Post Vaccination H.I. Titers of 144
Students With Five-Month Post Vaccination HI Titers of 25
 Students (Post Season).

| | % of persons with HI titer of | | | |
|---------------------|-------------------------------|----|-----|-----|
| | ≤8 | 16 | ≥32 | ≥64 |
| A/Shanghai - | | | | |
| Post vaccine | 3 | 4 | 93 | 85 |
| Post season | 2 | 20 | 68 | 36 |
| A/Taiwan - | | | | |
| Post vaccine | 2 | 4 | 94 | 83 |
| Post season | 12 | 20 | 68 | 52 |
| B/Yamagata - | | | | |
| Post vaccine | 4 | 3 | 93 | 89 |
| Post season | 12 | 20 | 68 | 48 |

Table 9

Comparison of One-Month Post Vaccination H.I. Titers of 46
Permanent Party With Five-Month Post Vaccination H.I. Titers
 of 25 Permanent Party (Post Season).

| | % of persons with HI titer of | | | |
|---------------------|-------------------------------|----|-----|-----|
| | ≤8 | 16 | ≥32 | ≥64 |
| A/Shanghai - | | | | |
| Post vaccine | 2 | 9 | 88 | 62 |
| Post season | 36 | 16 | 48 | 28 |
| A/Taiwan - | | | | |
| Post vaccine | 13 | 22 | 66 | 40 |
| Post season | 20 | 32 | 48 | 28 |
| B/Yamagata - | | | | |
| Post vaccine | - | 9 | 90 | 73 |
| Post season | 24 | 32 | 44 | 28 |

Table 10

Comparison of attack rates in vaccinated and
unvaccinated Air Force permanent party.

| <u>Vaccinated</u> | <u>Est. No. persons</u> | <u>No. of cases</u> | <u>Est. attack rates</u> | <u>Est. vaccine efficacy</u> |
|-------------------|-----------------------------|-------------------------|------------------------------|---|
| Yes | 3836 | 22 | 0.57 | $\frac{1.74 - .57}{1.74} = \frac{1.17}{1.74}$ |
| No | 288 | 5 | 1.74 | $\frac{1.17}{1.74} = 67\%$ |

Table 11

Estimated attack rates of influenza A (H3N2) in 4124
 permanent party with different accute HI antibody titers
 to A/Shanghai/11/87 at Lowry Air Force Base.

| <u>Titers</u> | <u>Est. # of persons</u> | <u># of cases</u> | <u>Est. attack Rate (%)</u> |
|---------------|------------------------------|-------------------|---------------------------------|
| ≤8 | 124 | 13 | 10.4 |
| 16 | 165 | 9 | 5.4 |
| 32 | 1350 | 5 | 0.4 |
| ≥64 | 2445 | 0 | 0.0 |
| TOTAL | 4124 | 27 | 0.7 |

Table 12

Estimated attack rates of influenza A (H3N2) in 2000
students with different acute HI antibody titers to
A/Shanghai/11/87 at Lowry Air Force Base.

| <u>Titers</u> | <u>Est. # of persons</u> | <u># of cases</u> | <u>Est. Attack Rate (%)</u> |
|---------------|------------------------------|-------------------|---------------------------------|
| ≤8 | 80 | 4 | 6.7 |
| 16 | 80 | 2 | 2.5 |
| 32 | 304 | 1 | 0.6 |
| ≥64 | 1536 | 1* | 0.3 |
| TOTAL | 2000 | 8 | 0.4 |

*This patient had been sick for 2 weeks when "acute" blood was drawn. All other patients had been sick 5 or less days.

Table 13
Comparison of results of virus isolation attempts
with results of CF and HI tests.

| <u>Students</u> | <u>Virus Isolation</u> | <u>CF Test</u> | <u>HI Test</u> |
|---------------------------|----------------------------|--------------------|--------------------|
| No. tested/ % positive | 1/8 ¹ 13% | 7/8 88% | 7/8 88% |
| <u>Perm. Party</u> | | | |
| No. tested/ % positive | 13/29 45% | 18/27 67% | 24/27 89% |
| <u>Total</u> | | | |
| No. tested/ % positive | 14/37 38% | 25/35 71% | 31/35 89% |

¹ Denominator represents total positive by virus isolation and/or serologic testing.

Table 14

No. of throat cultures positive for Group A
 betahemolytic streptococci in permanent party
 and students by weeks.

| <u>Week of</u> | <u>Students</u> | <u>Perm. Party</u> | <u>Total</u> |
|----------------|-----------------|------------------------|--------------|
| Nov. 6 | 1 | 0 | 1 |
| 13 | 0 | 0 | 0 |
| 20 | 1 | 0 | 1 |
| 27 | 0 | 0 | 0 |
| Dec. 4 | 1 | 0 | 1 |
| 11 | 1 | 1 | 2 |
| 18 | 1 | 1 | 2 |
| 25 | 1 | 1 | 2 |
| Jan. 1 | 0 | 1 | 1 |
| 8 | 1 | 1 | 2 |
| 15 | 0 | 1 | 1 |
| 22 | 1 | 2 | 3 |
| 29 | 3 | 1 | 4 |
| Feb. 5 | 0 | 0 | 0 |
| 12 | 1 | 4 | 5 |
| 19 | 2 | 1 | 3 |
| 26 | 1 | 0 | 1 |
| Mar. 5 | 3 | 1 | 4 |
| 12 | 2 | 2 | 4 |
| 19 | 1 | 0 | 1 |
| 26 | 0 | 1 | 1 |
| Apr. 2 | 0 | 1 | 1 |
| 9 | 0 | 1 | 1 |
| 16 | 1 | 1 | 2 |
| 23 | 0 | 1 | 1 |
| 30 | 1 | 0 | 1 |
| May 7 | 0 | 2 | 2 |
| 14 | <u>3</u> | <u>0</u> | <u>3</u> |
| | 26 | 24 | 50 |

Table 15

Number of confirmed cases of influenza at Lowry Air Force Base, 1982-1990.

| Year | Number of persons with indicated influenza virus | | | | | |
|---------|--|--------------------|----------------|--------------------|----------------|--------------------|
| | A H3N2 | | A H1N1 | | B | |
| | <u>Student</u> | <u>Perm. Party</u> | <u>Student</u> | <u>Perm. Party</u> | <u>Student</u> | <u>Perm. Party</u> |
| 1982-83 | 1 (0)* | 8 (0) | 14 (0) | 6 (0) | 0 | 11 (2) |
| 1983-84 | 0 | 0 | 12 (0) | 20 (0) | 14 (0) | 56 (13) |
| 1984-85 | 4 (0) | 32 (9) | 0 | 0 | 0 | 2 (0) |
| 1985-86 | 2 (0) | 14 (2) | 0 | 0 | 48 (1) | 78 (9) |
| 1986-87 | 0 | 0 | 23 (0) | 98 (15) | 0 | 0 |
| 1987-88 | 0 | 10 (0) | 0 | 0 | 0 | 3 (0) |
| 1988-89 | 0 | 1 (0) | 6 | 33 (5) | 6 (0) | 16 (4) |
| 1989-90 | 8 (4) | 29 (5) | 0 | 0 | 0 | 0 |
| 1990-91 | 0 | 1 (0) | 0 | 0 | 4 (0) | 17 (1) |

*() number in parentheses indicates the number who did not receive vaccine.

ADDENDUM I.**Outbreak of Influenza B - 1990-1991**

The main body of the report has dealt with A/H3N2 which occurred at Lowry Air Force Base in 1989-1990. During the following year we had an influenza B outbreak in 1990-1991. We have only preliminary data, and will provide additional data in subsequent reports.

In January and February 1991 influenza B appeared in Colorado, and was responsible for 21 identified cases at Lowry Air Force Base. Four of these occurred among approximately 2,000 students (attack rate 0.2%), and 17 occurred in approximately 3,900 permanent party (attack rate .43%). Many aspects of this outbreak have not yet been worked out, and a detailed report will be coming in the near future.

ADDENDUM II.**Spring Outbreak of Influenza A at the Air Force Academy**

In the late spring of 1991 an outbreak of influenza A/H3N2 occurred at the Air Force Academy. An influenza A/H3N2 virus was isolated at the EPI lab at Brooke Air Force Base, Texas. Samples of serum pairs from individuals who were sick at the Academy were sent to Denver. Of particular interest was the relationship of this virus to the A/Shanghai/16/88 virus which was the A/H3N2 component in the vaccine used in 1990. C.F. tests were run for influenza A and B, and H.I. tests were run for the A/Shanghai/16/88, A/Beijing/353/89 (a component of next year's vaccine), A/Colorado/1/89, which was isolated from a 17 year old patient in Brighton, Colorado (also a late spring isolate), and A/Colorado/443/91, which was isolated from the Air Force Academy.

In the recruits we found a reasonably good response to all the strains. The two Colorado strains appear to be closely related, and resemble A/Beijing/353/89 more than A/Shanghai/16/81.

In the same test, the results with sera from permanent party who had been vaccinated the year previously with A/Shanghai/16/88 are disappointing. We would also emphasize that with each serum pair the results with the two current Colorado viruses are much closer to those obtained with the A/Beijing/303/89 strain than with the A/Shanghai/16/88 strain.

It is of considerable interest that 6 or more of the 20 patients from the Academy failed to show increases in titer to any of the A/H3N2 viruses used in the test. It would be of interest to test them for RSV, para influenza 1, 2, and 3, and possibly other respiratory viruses.